REMARKS/ARGUMENTS

This Amendment is being filed in response to the Final Office Action mailed on August 24, 2011 from the U.S. Patent and Trademark Office, in which claims 1-3, 5, 6, 8, 11-15, 17-37, 39-46, 48-53, 55, 57-60 and 63 were rejected. With this Amendment, claims 1 and 45 have been amended. Support for the claim amendments are found throughout Applicants' as-filed application, including at least at paragraphs [0030], [0049], [0050] and [0067], as well as Examples 2-4 in paragraphs [0114] - [0122] in US Publication 2004/0197323. No new matter is added with this Amendment. Thus, Applicants respectfully request reconsideration and allowance of pending claims 1-3, 5, 6, 8, 11-15, 17-37, 39-46, 48-53, 55, 57-60 and 63.

The Final Office Action rejected claims 1, 5, 6, 17-19, 40 and 41 under 35 U.S.C. § 102(b) as allegedly being anticipated by *Biochemistry*, Vol. 34, pages 8835-8842 to Neugebauer et al. ("Neugebauer"). The Final Office Action has rejected claims 1-3, 5, 6, 8, 12-15, 17-37, 39-41, 43-46, 49-51, 55, 57-59 and 63 under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,086,918 to Stern et al. ("Stern") in view of U.S. Patent No. 5,120,712 to Habener ("Habener"), U.S. Publication No. 2003/0104981 to Mandic ("Mandic") or U.S. Patent No. 6,110,892 to Barbier et al. ("Barbier"). The Final Office Action rejected claims 3 and 48 under 35 U.S.C. § 103(a) as allegedly being obvious over Stern in view of Habener, Mandic or Barbier as applied against claims 1-3, 5, 6, 8, 12-15, 17-37, 39-41, 43-46, 49-51, 55, 57-59 and 63 above, and further in view of U.S. Patent No. 5,912,014 to Stern et al ("the '014 patent"). The Final Office Action rejected claims 1-3, 5, 6, 8, 11-15, 17-37, 39-41, 43-46, 49-53, 55, 57-59 and 63 under 35 U.S.C. § 103(a) as allegedly being obvious over PCT Publication No. WO 02/043767 ("the '767 Application") in view of Habener, Mandic or Barbier. The Final Office Action rejected claims 5 and 48 under 35 U.S.C. § 103(a) as allegedly being obvious over the '767 Application in view of Habener, Mandic or Barbier as applied against claims 1-3, 5, 6, 8, 11-15, 17-37, 39-41, 43-46, 49-53, 55, 57-59 and 63 above, and further in view of the '014 patent.

Rejections Under 35 U.S.C. § 102(b)

The Final Office Action rejected claims 1, 5, 6, 17-19, 40 and 41 under 35 U.S.C. § 102(b) as allegedly being anticipated by Neugebauer. The Final Office Action states on page 9:

"The examiner agrees that claims limited to tablet or capsule administration forms would not be anticipated by or obvious over the Neugebauer et al article."

While it is believed that the prior claims were patentable in view of the cited art, out of an abundance of caution, pending independent claim 1 has been amended hereby to recite, *inter alia*, the following:

- "An oral pharmaceutical composition **in the form of a tablet or a capsule for** enhancing bioavailability and absorption of an active peptide agent comprising…" (emphasis added)

Therefore, it is respectfully submitted that the rejection of pending claims 1, 5, 6, 17-19, 40 and 41 under 35 U.S.C. § 102(b) as allegedly being anticipated by Neugebauer has been overcome. Thus, reconsideration and allowance of pending claims 1, 5, 6, 17-19, 40 and 41 is respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

The Final Office Action has rejected claims 1-3, 5, 6, 8, 12-15, 17-37, 39-41, 43-46, 49-51, 55, 57-59 and 63 under 35 U.S.C. § 103(a) as allegedly being obvious over Stern in view of Habener, Mandic or Barbier. While it is believed that the prior claims were patentable in view of the cited art, out of an abundance of caution, pending independent claim 1 has been amended hereby to recite, *inter alia*, the following:

- "An oral pharmaceutical composition in the form of a tablet or a capsule for enhancing bioavailability and absorption of an active peptide agent comprising: an amidated active peptide agent, wherein the amidated active peptide agent ~~that~~ has been amidated such that an amide group has been added at ~~its~~ a C-terminus of an active peptide agent that~~, and~~ is not found in nature with an amide group at its C-terminus;~~, said composition further comprising~~ and an absorption enhancer effective to promote bioavailability of said amidated active peptide agent, or a pharmaceutically acceptable pH-lowering agent that is present in said pharmaceutical composition in a quantity which, if said composition were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 5.5, wherein the composition enhances bioavailability and absorption of the amidated active peptide agent as compared with an oral pharmaceutical composition comprising the same active peptide agent having a free acid at its C-terminus instead of an amide group at its C-terminus."

Pending independent claim 45 has been amended hereby to recite, *inter alia*, the following:

- "A method for ~~modifying a physiologically active peptide to increase its~~ enhancing oral bioavailability and absorption of a physiologically active peptide, while substantially maintaining its physiological activity, said method comprising: amidating ~~a~~ the physiologically active peptide to create an amidated peptide having an amide group at its C-terminus, wherein the physiologically active peptide ~~that~~ is not ~~naturally amidated~~ found in nature with an amide group at its C-terminus~~ at said C-terminus~~; and orally administering said amidated peptide in combination with (i) at least one absorption enhancer effective to promote bioavailability of said amidated peptide, or (ii) a pH-lowering agent that is present in said pharmaceutical composition in a quantity which, if said composition were added to ten milliliters of 0.1 M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 5.5, wherein the bioavailability and absorption of the amidated peptide is enhanced as compared with the same active peptide having a free acid at its C-terminus instead of an amide group at its C-terminus"

Support for the amendments to independent claims 1 and 45 are found throughout Applicants' as-filed application, including at least at paragraphs [0030], [0049], [0050] and [0067], as well as Examples 2-4 in US Publication 2004/0197323, paragraphs [0114] - [0122].

Applicants amended independent claim 1 recites, "[a]n oral pharmaceutical composition **in the form of a tablet or a capsule for enhancing bioavailability and absorption of an active peptide agent**." To that end, the oral **pharmaceutical composition comprises** "**an amidated active peptide agent**, wherein the amidated active peptide agent has been amidated such that **an amide group has been added at the C-terminus of an active peptide agent that is not found in nature with an amide group at its C-terminus**"; and "**an absorption enhancer** effective to promote bioavailability of said amidated active peptide agent, **or a pharmaceutically acceptable pH-lowering agent**." **The "composition enhances bioavailability and absorption of the amidated active peptide agent as compared with an oral pharmaceutical composition comprising the same active peptide agent having a free acid at its C-terminus instead of an amide group at its C-terminus**." (emphasis added).

The Final Office Action states on page 8: "The examiner agrees that Habener, Mandic, and Barbier et al teach non-amidated peptides as well as amidated peptide" and "The examiner

agrees that none of the secondary references disclose or suggest the selective use of C-terminal amidated peptides in the oral delivery system of the primary references."

In addition, the Final Office Action states on pages 8-9: "To the extent that Applicants are arguing that C-terminally amidated peptides have unexpectedly higher therapeutic activity upon oral administration than do the corresponding non-amidated peptides, Applicants have not submitted evidence which demonstrates this assertion either for peptides in general or for the particular peptides taught by Habener, Mandic, and Barbier et al." Applicants respectfully disagree.

Applicants' compositions comprising amidated peptides do have unexpectedly higher therapeutic activity upon oral administration than do the corresponding non-amidated peptides, and the as-filed application provides evidence thereof. Examples 2-4 in the as-filed application (Paragraphs [0114] - [0122] in US Publication 2004/0197323), for example, illustrate means or ways by which this desired result is achieved. For example, in Example 3 of the as-filed application (Paragraphs [0119] - [0120] in US Publication 2004/0197323), the bioavailability and absorption of an analog of Parathyroid Hormone, PTH1-34, with or without a C-terminal amide group was compared. A pharmaceutical composition comprising PTH1-34-OH (0.5 mg/ml) (the active peptide having a free acid at its C-terminus) and a pharmaceutical composition comprising PTH1-34NH_2 (0.5 mg/ml), each additionally containing citric acid (0.5 M), lauroylcarnitine (10 mg/ml) and salmon calcitonin (included as an internal marker) (0.5 mg/ml), was injected directly into the exposed duodenum of rats. The maximum concentration of PTH 1-34-OH was 3.05 ng/ml and that of PTH1-34NH_2 was 26.7 ng/ml, which was nearly 9 times greater than the free acid form of PTH (1-34). After 60 minutes, the concentration of PTH1-34NH_2 was still nearly 9 times greater than that of PTH1-34-OH (**see Table 8 reproduced below**). The absolute bioavailability of PTH1-34NH_2 was 3.68% and that of PTH1-34-OH was 0.45%. Table 8 illustrates the significantly enhanced bioavailability and absorption that C-terminal amidation imparts to the active peptide PTH as compared to the free acid form of PTH.

TABLE 8

Effect of C-Terminal Amide on the Pharmacokinetic Profile of PTH1-34

Time (Min)	PTH1-34-OH ng/ml ± standard error	PTH1-34NH_2 ng/ml ± standard error
0	0.00	0.00
5	2.69 ± 1.35	26.70 ± 7.84
15	3.05 ± 1.31	21.03 ± 4.07
30	1.90 ± 0.81	13.13 ± 3.36
60	0.62 ± 0.38	5.39 ± 3.08

TABLE 8-continued

Effect of C-Terminal Amide on the Pharmacokinetic Profile of PTH1-34

Time (Min)	PTH1-34-OH ng/ml ± standard error	PTH1-34NH_2 ng/ml ± standard error
120	0.81 ± 0.35	1.18 ± 1.08
Absolute Bioavailability (%)	0.45 ± 0.19	3.68 ± 0.76

In addition, in Applicants' as-filed application, Applicants provided several other examples, wherein enhanced bioavailability and absorption has been demonstrated for a pharmaceutical composition comprising a peptide amidated at a location not naturally amidated and an absorption enhancer or a pH-lowering agent; in comparison to the results achieved with a pharmaceutical composition comprising a peptide in the free acid form and an absorption enhancer or a pH-lowering agent.

The cited references, alone or in combination, neither teach, disclose, or suggest the limitations expressly recited in independent claim 1, as amended herein, wherein the combination of the amidated active peptide and an absorption enhancer or a pH-lowering agent, enhances bioavailability and absorption of the amidated active peptide as compared with an oral pharmaceutical composition comprising the same active peptide having a free acid at its C-terminus. Thus, it is respectfully requested that the Examiner reconsider and withdraw the rejection of independent claim 1. Lastly, as dependent claims 2-3, 5, 6, 8, 12-15, 17-37, 39-41 and 43-44 all depend from amended independent claim 1, the arguments noted above are all equally applicable to the these dependent claims. Thus, reconsideration and allowance of pending claims 1-3, 5, 6, 8, 12-15, 17-37, 39-41 and 43-44 is respectfully requested.

Pending independent claim 45 includes similar amendments as amended independent claim 1, and is believed to be patentable for at least the same reasons as amended independent claim 1. As dependent claims 46, 49-51, 55, 57-59 and 63 all depend from amended independent claim 45, the arguments noted above are all equally applicable to the these dependent claims. Thus, reconsideration and allowance of pending claims 45-46, 49-51, 55, 57-59 and 63 is respectfully requested.

The Final Office Action rejected claims 3 and 48 under 35 U.S.C. § 103(a) as being obvious over Stern in view of Habener, Mandic or Barbier as applied against claims 1-3, 5, 6, 8, 12-15, 17-37, 39-41, 43-46, 49-51, 55, 57-59 and 63 above, and further in view of the '014 patent. Claim 3 depends from amended independent claim 1. The '014 patent does not cure the deficiencies of Stern, Habener, Mandic or Barbier. Thus, dependent claim 3 is believed to be patentable. Claim 48 depends from amended independent claim 45. The '014 patent does not cure the deficiencies of Stern, Habener, Mandic or Barbier. Thus, dependent claim 48 is

believed to be patentable. Thus, reconsideration and allowance of dependent claims 3 and 48 is respectfully requested.

The Final Office Action rejected claims 1-3, 5, 6, 8, 11-15, 17-37, 39-41, 43-46, 49-53, 55, 57-59 and 63 under 35 U.S.C. § 103(a) as being obvious over the '767 Application in view of Habener, Mandic or Barbier. As discussed above, Applicants' compositions comprising amidated peptides do have unexpectedly higher therapeutic activity upon oral administration than do the corresponding non-amidated peptides, and the as-filed application provides evidence thereof, see for example, Examples 2-4 in US Publication 2004/0197323, paragraphs [0114] - [0122]. The cited references, alone or in combination, neither teach, disclose, or suggest the limitations expressly recited in independent claim 1, as amended herein, wherein the combination of the amidated active peptide and an absorption enhancer or a pH-lowering agent, enhances bioavailability and absorption of the amidated active peptide as compared with an oral pharmaceutical composition comprising the same active peptide having a free acid at its C-terminus. Thus, it is respectfully requested that the Examiner reconsider and withdraw the rejection of independent claim 1. Lastly, as dependent claims 2-3, 5, 6, 8, 11-15, 17-37, 39-41 and 43-44 all depend from amended independent claim 1, the arguments noted above are all equally applicable to the these dependent claims. Thus, reconsideration and allowance of pending claims 1-3, 5, 6, 8, 11-15, 17-37, 39-41 and 43-44 is respectfully requested.

Pending independent claim 45 includes similar amendments as amended independent claim 1, and are believed to be patentable for at least the same reasons as amended independent claim 1. As dependent claims 46, 49-53, 55, 57-59 and 63 all depend from amended independent claim 45, the arguments noted above are all equally applicable to the these dependent claims. Thus, reconsideration and allowance of pending claims 45-46, 49-53, 55, 57-59 and 63 is respectfully requested.

The Final Office Action rejected claims 5 and 48 under 35 U.S.C. § 103(a) as being obvious over the '767 Application in view of Habener, Mandic or Barbier as applied against claims 1-3, 5, 6, 8, 11-15, 17-37, 39-41, 43-46, 49-53, 55, 57-59 and 63 above, and further in view of the '014 patent. Claim 5 depends from amended independent claim 1. The '014 patent does not cure the deficiencies of the '767 Application, Habener, Mandic or Barbier. Thus, dependent claim 5 is believed to be patentable. Claim 48 depends from amended independent

claim 45. The '767 Application does not cure the deficiencies of Stern, Habener, Mandic or Barbier. Thus, dependent claim 48 is believed to be patentable. Thus, reconsideration and allowance of dependent claims 5 and 48 is respectfully requested.

CONCLUSION

Applicants have made an earnest effort to respond to all issues raised in the Final Office Action of August 24, 2011, and to place all claims presented in condition for allowance. No amendment made herein was for the purpose of narrowing the scope of any claim, unless Applicants have argued herein that such amendment was made to distinguish over a particular reference or combination of references.

Applicants submit that pending claims 1-3, 5, 6, 8, 11-15, 17-37, 39-46, 48-53, 55, 57-60 and 63 have been placed in condition for allowance, and respectfully requests an early and favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Applicants believe that no fees are required in connection with the paper transmitted herewith. However, if any fees are due, Applicant authorizes the Commissioner for Patents to charge these fees to Deposit Account No. 50-1561, Reference No. 133302-546280/US.

Respectfully submitted,

Date: October 24, 2011

/Danielle T. Abramson/

Danielle T. Abramson, Ph.D., Reg. No.: 52,539
David J. Dykeman, Reg. No.: 46,678
Customer No.: 67395
Greenberg Traurig, LLP
200 Park Avenue
P.O. Box 677
Florham Park, NJ 07932-0677
Tel: 973-443-3576
NJDocket@gtlaw.com